REMARKS/ARGUMENTS

Support for the amendment to claim 1 is provided at e.g., p. 34, line 13-24. The amendment should not be construed as acquiescence in any ground of rejection. Applicants address the office action's comments using the paragraph numbering of the office action.

5-6. Claims 1, 49, 50, 52, 53, 56, 66 and 68 stand rejected as anticipated Boyer. This rejection is based on an interpretation of the claims in which the phrase "preferentially generates the signal" is alleged to be a preference in the mind of the experimenter. Applicants maintain that this is a misinterpretation of the claim for the reasons described in the previous response. Nevertheless, claim 1 has been amended in an attempt to overcome this issue. The amendment specifies that if the reporter comprises a fluorophore, the fluorophore is linked via a cleavable linker to a quencher which quenches fluorescence. On entering the cell, the quencher is cleaved, thereby allowing the reporter to preferentially generate a signal once inside the cell. Boyer does not disclose linking a fluorophore via a cleavable linker to a quencher. Thus, the rejection is moot.

7. Claims 1, 3, 14-16, 25-35, 37, 40, 46-50, 52, 53, 56, 58, 66 and 68 stand rejected as obvious over Boyer in view of Schaeffer or Thompson. This rejection is respectfully traversed.

The office action acknowledges that motivation is required for combining the references (sentence bridging pp. 14-15). However, the office action does not appear to recognize that the motivation must be specific to the claimed invention. "To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the *specific* combination that was made by the applicant." *In re Dance,* 160 F.3d 1339, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis supplied). The motivation must be specific and objective. *In re Dembiczak,* 50 USPQ2d 1614 (Fed. Cir. 1999). The motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood,* 28 USPQ2d 1300, 1302 (BPAI 1993).

Here, the office action has simply pointed to certain advantages of using luciferin relative to luciferase in an immunoassay (Schaeffer). However, it would not have been apparent that the advantages of luciferin relative to luciferase in an immunoassay would translate into advantages of luciferin relative to a fluorophore in a transport assay given the different context in which luciferin would have to be transported by a transporter into a cell tethered to a compound and be metabolized by a luciferase within the cell. If the luciferin interfered with the capacity of a compound to enter the cell via a transporter, it would decrease sensitivity. Even if, as the office action proposes, the artisan would have realized that the advantages of luciferin in an immunoassay were not confined to an immunoassay, this does not necessarily imply that the artisan would have been motivated to employ luciferin in the specific context of the claimed transport assays. Likewise, the office action has not identified anything within Boyer that would have prompted the artisan to look for improvements on Boyer's assay. Even if the artisan were to have scoured the literature with a general goal of improving the transport assay without such prompting, it does not mean that he would have selected luciferin as the means to do so.

With respect to Thompson's use of luciferase as means of selecting transformants in a gene shuffling procedure, the office action originally pointed to an alleged advantage of Thompson's method that it can be practiced on organisms that do not grow well as a motivation for combining Thompson with Boyer. As applicants have previously noted, whether organisms grow well in a gene shuffling protocol provides no motivation to transmute use of luciferin/luciferase from the standard context of selecting transformants to the entirely different context of transporter assays, which do not require selection of transformants.

The office action now points to Thompson's disclosure of high throughput screening as an alternate motivation for combination of the references citing to col. 22, line 25 and col. 36, line 23. Applicants do not find disclosure of high throughput screening at these places of the patent; merely a list of markers for recognizing transformants, of which luciferase is one. In any event, an observation that luciferase and other markers enable one to perform high throughput screening in a gene shuffling protocol through recognition of genetically transformed cells does not suggest that luciferase be used in a transport assay not requiring genetic

transformation. The benefit of easily recognizing genetic transformants is that of Thompson's own method, not that of the combination of Thompson with Boyer.

The office action also points to Thompson's reference to certain transporters at col. 24 as evidence of the motivation to combine Thompson with Boyer. Thompson's discussion of transporters is as possible goal of his shuffling procedure to equip certain cells with transporters so they might better expel certain toxic products from gene libraries. This discussion is unrelated to Thompson's discussion of luciferase in a list of markers for recognizing transformants, or Boyer's assays for measuring transporter function. Thus, Thompson's discussion of transporters did not provide specific motivation to combine Thompson with Boyer so as to achieve the claimed invention.

The office action notes that MPEP 2144 provides that there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention and argues based on this that no connection between the cited references is required. Applicants agree that the motivation for combining the references need not be the same as applicants'. However, whether the motivation is the same or different from that of applicants, it must be specific to the claimed invention, as discussed above.

Further, applicants have not argued that the cited references are nonanalogous art. Rather, applicants' position is that it necessary but not sufficient that references be from analogous art. References from analogous art cannot be combined without specific motivation, as discussed above. *In re Paulson,* cited throughout the office action, addresses only the issue of what constitutes analogous art, and provides no support for dispensing with motivation specific to the claimed invention.

Claims 25, 27 and 35 specify that the claimed methods are performed on different cells in the same reaction vessels. The office action alleges these claims are obvious in view of Thompson's reference to mixed populations of library cells or mixed populations of library cells and indicator cells in a gene shuffling procedure in combination with Boyer. Applicants previously pointed out that although in some contexts, it is known to mix cells, what is at issue is whether it would have been obvious to do so in the claimed methods. The context of

Thompson's mixing cells is entirely different. Thompson mixes cells either in generating or screening expression libraries resulting from gene shuffling. No reason has been provided that the artisan would have seen any connection between whether Thompson does or does not mix cells in the generation and screening of shuffled gene libraries with whether mixtures of cells should be used in screening compounds for capacity to be transported into cells.

In reply the office action alleges that no connection is required between the references citing to MPEP 2144. Applicants do not dispute the teaching of MPEP2144 that the motivation for combining the references can be different from that which motivated the inventors toward the claimed invention. Nevertheless, whether the motivation is the same or different than that of the inventors, it must be such as to have motivated one to the specific claimed combination and with sufficient force to have impelled the artisan to that combination. Here, the office action is relying on a motivation different from that of the present inventors, namely, that mixing of cells is useful in a gene shuffling procedure. However, this information is of no apparent relevance to assaying a transporter in which the goal is not to create and identify recombinant DNA sequences having improved properties but to determine whether a compound can pass through a transporter. Thus, the asserted motivation is one for performing Thompson own method, not a motivation that would have impelled the artisan to combine Thompson with Boyer.

Claims 28-34 and 40 are distinguished for similar reasons as discussed in the previous response. As these remarks do not appear to have been specifically addressed in the present office action, they are repeated here. The Office Action alleges that the combined references of Schaeffer and Thompson) teach different strains, and epitopes (although the Office Action provides citations only to Thompson). Again, it is not disputed that different strains of cells are known and that strains can be distinguished by different epitopes as markers. What is at issue is whether it would have been obvious to use such different strains in the context of the claimed methods. In the claimed methods, the use of distinguishable strains or markers facilitates simultaneous assays of transport into different cells in the same vessel by allowing the different cells to be distinguished. Thompson uses different strains for an entirely different

purpose, namely, to generate diversity in gene shuffling assays. No motivation has been provided as to why the artisan would see any relevance of the use of diverse strains for gene shuffling with the use of different strains to allow multiple transport assays to be conducted simultaneously in the same vessel.

Claim 46 is distinguished for analogous reasons as discussed in the previous response. Because the present office action does not appear to have addressed applicants' position with respect to this claims, these remarks are reiterated here. Claim 46 specifies a method containing steps of providing and screening a focused library where the focused library contains variants of a compound shows to be a substrate for a transporter in a previous step. The Office Action alleges that such is suggested by the combined disclosure of Schaeffer and Thompson, but again the Office Action provides citations only to Thompson. Thompson discusses enriching a shuffled DNA library for members having a desired property by screening. Again, it is not apparent how an artisan would see any connection between such teaching and methods employing variants of a compound in assays for a substrate of a transporter.

Claim 48 is directed to an isolated DNA molecule encoding a carrier-type transporter from a cell that has been shown to transport a compound. The Office Action alleges that Thompson discloses the isolation of unknown expression products by HTS techniques. Thompson merely discloses that "High-throughput screening processes can be used e.g., macrodroplet sorting, fluorescence activated cell sorting or magnetic activated cell sorting, to identify and isolated the desired organisms in a combinatorial gene expression library" (col. 5, lines 60-65). Again, it is not disputed that high throughput processes are known or that genes can be isolated from expression libraries. What is at issue is whether the artisan would have been motivated to, and known how to, modify the teaching of Boyer from a method of identifying a substrate of a known transporter, into a method of identifying a hitherto unknown transporter for a known compound. As the Federal Circuit has cautioned, a "person of ordinary skill is the art is...*presumed to be one who thinks along the lines of conventional wisdom in the art...*," *Standard Oil Co. v American Cyanamid Co.*, 774 F.2d 448 (Fed. Cir. 1985), at p. 454 (emphasis added). Knowledge of standard but general techniques such as expression cloning and

high throughput screening is not enough for the artisan to depart from conventional wisdom in the art to achieve the claimed invention.

The office action disagrees with applicants' position on the basis that *Standard Oil* is irrelevant, and that in any event the combined teachings of Schaeffer and Thompson clearly represent what was conventional in the art at the time of filing and thus modification of the Boyer reference is appropriate.

In reply, the *Standard Oil* case is relevant in showing the limited capability of the artisan in being confined to think along the lines of conventional wisdom in the art. Applicants, for the sake of discussion, will agree that the teachings of Schaeffer and Thompson individually represent conventional wisdom in the art, and that the artisan is capable of following such conventional wisdom in the art. However, the combination of either of these references with Boyer is an entirely different matter. Such a combination requires isolating a small part of the teaching of Thompson from a gene shuffling protocol and using this in an entirely different context to modify an assay for a known transporter into a means for identifying an unknown transporter. The synthesis of diverse areas of investigation to arrive at new combinations having hitherto unrecognized advantages is not the province of the artisan confined to conventional wisdom, but is rather the hallmark of true invention

For these reasons, it is respectfully requested that the rejections be withdrawn.

9. Claims 1, 49, 50 and 66 stand rejected as anticipated by Schramm. This rejection is respectfully traversed particularly insofar as it might be applied to the amended claims.

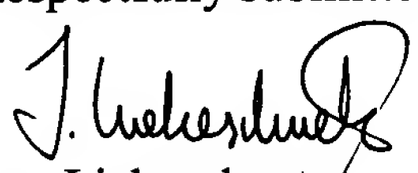
Schramm discusses an assay for detecting transport of fluorescently conjugated bile salts through liver cells. Separately, Schramm mentions that binding of his fluorophore to serum albumin causes an increase in its emissions. Serum albumin is a serum protein present outside cells. It is not clear from Schramm whether liver cells contain any protein with similar charge characteristics to serum albumin that would bind to the fluorophore within cells. Thus, it is unclear whether the signal from Schramm's fluorophore undergoes any detectable change on entering cells.

In any event, Schramm does not disclose a reporter comprising a fluorophore linked to a quencher via a cleavable linker, which is cleaved after entry into the well. The serum albumin mentioned by Schramm is not a quencher, is not linked via a cleavable linker, and is not removed within the cells.

Therefore, it is respectfully submitted that the rejection should be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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Attachments
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